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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,742	DOEKEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-26* is/are pending in the application.

4a) Of the above claim(s) *14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4-13,26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-2, 4-26 are pending.

Applicant's amendment of claims 1-2, 4-13, 26, cancellation of claim 3, submission of a new sequence listing in electronic and paper form, and submission of alignments, in a communication filed on 8/5/2004 are acknowledged.

As indicated in the previous Office Action mailed on 4/6/2004, claims 14-25 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected with traverse in a communication filed on 1/9/2004. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. As shown in the Interview Summary of 8/2/2004, the Examiner indicated that a signed copy of an IDS filed on 1/23/2002 will be submitted to Applicants with this communication. It is noted, however, that a careful review of the record shows that the Examiner provided Applicants with a signed copy of that IDS in the Office Action mailed on 9/9/2003 (Paper No. 11). See PTO form 326 mailed with that Office Action and paragraph 6 of the Office Action. Applicants may obtain a copy of the signed IDS from either Private PAIR or Public PAIR under the document description "List of References cited by Applicants" dated 9/9/2003 (http://pair-direct.uspto.gov).

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-2, 4-13, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 1 and 26 (claims 2, 4-13 dependent thereon) are indefinite in the recitation of "are identifiable by having at least substantial structural homology with the core motifs having SEQ ID NO: ...." as the term "substantial" is a relative term and neither the claim nor the specification provide a standard for ascertaining the requisite degree. As written, one cannot determine how much structural homology is encompassed by the term (e.g. % sequence identity). Therefore one of skill in the art cannot reasonably apprised of the scope of the invention. For examination purposes, it will be assumed that the term reads "are identifiable by having any % sequence identity to the core motifs of SEQ ID NO: ..... ". Correction is required.

5. Claim 26 is indefinite in the recitation of "wherein the adenylation domains are identifiable .....found in naturally occurring ...." for the following reasons. As indicated in paragraph 84 of the specification (US Patent Application Publication No. 2002/0064834), the B. subtilis ATCC 21332 gene srfA-B encodes at least the adenylation domain recognizing Asp and the B. brevis ATCC 8185 tycA gene encodes the adenylation domain recognizing Phe, therefore it is unclear as to how the term further limits the adenylation domains if they are already defined by their source, i.e. B. subtilis ATCC 21332 srfA-B and B. brevis ATCC 8185 tycA genes. For examination purposes, no patentable weight will be given to the term. Correction is required.

6. Claim 2 was rejected as being indefinite due to the recitation of the term "condensation domain...is covalently bound to the module...". In view of Applicant's definition of the term in page 11, lines 20-32 of the specification, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-2, 4-13 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in a previous Office Action mailed on 4/6/2004.

9. According to Applicants, the presentation of alignment data in a personal interview with Applicant's representative on 8/2/2004, was found persuasive in regard to the enablement and written description rejections previously applied so long as the claims were modified to include some structural features which have some correlation with known adenylation domains (A domains). Applicants argue that the claims have been amended to include structural features which bear correlation with known adenylation domains. In particular, Applicants refer to alignments of known adenylation domains wherein consensus sequences have been determined. According to Applicants, these consensus sequences (core motifs A1-A10) are representative of the sequences for adenylation domains which have specificity for amino acids other than Asp and Phe. Applicants indicate that "substantial structural homology" would include variations in all or some of the core motifs (consensus sequences) and assert that these variations are within the scope of the invention. Applicants also assert that the information provided is sufficient to identify a sequence as an adenylation domain. Applicants also argue that due to the co-linearity of peptide synthetases, it is relatively routine to identify the adenylation domain for a particular amino acid once the sequence of the polypeptide produced by a particular non-ribosomal peptide synthetase is known. Applicants refer to the teachings of Marahiel et al. and Stachelhaus et al. in

support of the argument that it would not require undue experimentation to identify A-domains that recognize Asp and Phe, and to construct the two minimal modules as set forth in the claims.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejections. The Examiner acknowledges the alignments presented in the personal interview and also submitted with Applicant's response of 8/5/2004. However, for the record, it is noted that the Examiner did not find the alignments presented persuasive to overcome the 35 USC 112, first paragraph rejections previously applied so long as the claims were modified to include only structural features which have some correlation with known adenylation domains (A domains). As indicated in the previous Office Action, the claimed invention requires not only a genus of adenylation domains but also condensation domains, thiolation domains, and thioesterase domains from any non-ribosomal peptide synthetase. Therefore, even if the claims were found to be adequately described in regard to a genus of adenylation domains by recitation of structural elements common to members of the genus, which features constitute a substantial portion of the genus, the claims would not be adequately described in regard to the genus of condensation domains, thiolation domains, and thioesterase domains also required in the claimed invention.

It is reiterated herein that while claim 26 would be adequately described in regard to the adenylation domains encoded by the srfA-B gene from B. subtilis ATCC 21332 and tycA gene from B. brevis ATCC 8185, the claim is not adequately described in regard to the genus of condensation domains, thiolation domains and thioesterases domains encompassed by the claim. The claim would be adequately described in regard to the condensation domains if the gene encoding the domain used in the constructs described in paragraphs 104-176 (US Patent Application Publication No. 2002/0064834) is indicated in the claim. It is noted however that it is unclear from the specification as to the source of the condensation domain in the constructs described in paragraphs 104-176. It appears from the specification (paragraph 84; US Patent Application Publication No. 2002/0064834) that the claim would be adequately described

regarding thioesterase and thiolation domains if it is indicated that those domains are encoded by the srfA-C gene from B. subtilis ATCC 21332.

While the Examiner acknowledges the amendments to the claims, it is noted that while claims 1-2, 4-13 refer to "adenylation domains identifiable by having at least substantial structural homology with the core motifs having SEQ ID NO: 1-10 found in naturally occurring non-ribosomal peptide synthetases", the core motifs of SEQ ID NO: 1-10, this amendment is not sufficient to overcome the written description rejection in regard to the genus of adenylation domains required in the claimed invention. First, the term as written does not indicate that the genus of adenylation domains recited must share any structural feature. Instead, the term indicates that the genus of adenylation domains can be identified (i.e. identifiable) by determining whether they have any structural homology (as interpreted) to the core motifs of SEQ ID NO: 1-10. The term "identifiable" cannot be construed as defining the genus of adenylation domains by structure. The genus of adenylation domains recited does not appear to exclude adenylation domains which lack structural homology to the core motifs of SEQ ID NO: 1-10. Thus, the species in the genus of adenylation domains recited in the claims do not share any meaningful structural features. In addition, as extensively discussed above, term "substantial structural homology" has been found indefinite. Therefore, since one of skill in the art cannot determine the meets and bounds of what is encompassed by the term "substantial structural homology", it is unclear as to how one of skill in the art can reasonably conclude that any level of variation in some of the core motifs is within the scope of the invention, particularly in view of the fact that there is no information as to the level of variation in these core motifs found in naturally occurring non-ribosomal peptide synthetases.

In regard to the teachings of Marahiel et al. and Stachelhaus et al., as well as arguments indicating that it would be routine to identify A-domains for a particular amino acid once a polypeptide produced by a particular non-ribosomal peptide synthetase is known, it is noted that, as asserted by Applicants, the core motifs of A1-A10 appear to be common to all dipeptide synthetases. Therefore, in the absence of

some structural features known to be characteristic of adenylation domains which recognize Asp and Phe, it is unclear as to how one of skill in the art can recognize which A-domains are specific for Asp and Phe as required by the claims. While one could argue that the motifs of A1-A10, in addition with structural features of known A-domains specific for Asp and Phe, would constitute structural features which describe a substantial portion of the genus of adenylation domains required, the instant claims do not recite these structural features. Therefore, for the reasons set forth above, one cannot reasonably conclude that the claimed invention is adequately described.

11. Claims 1-2, 4-13 and 26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for the production of Asp-Phe using a hybrid Asp-Phe dipeptide synthetase, wherein the dipeptide synthetase comprises two minimal modules and a thioesterase domain, wherein one of the minimal modules recognizes L-Asp and the other minimal module recognizes L-Phe, wherein the minimal modules are connected by a condensation domain, wherein the minimal module recognizing L-Phe is covalently bound at its N-terminal end to the condensation domain, wherein each of these minimal modules comprise an adenylation domain and a thiolation domain containing a 4'phosphopantetheinyl cofactor, and wherein the adenylation, thiolation, condensation and thioesterase domains are encoded by the srfA-B and the srfA-C genes from B. subtilis ATCC 21332 (encoding surfactin synthetase) and/or the tyc operon (encoding tyrocidine synthetase) from B. brevis ATCC 8185, and (2) the method of (1) wherein a thioesterase type II is also used in addition to the dipeptide synthetase, does not reasonably provide enablement for the method described above in (1) or (2) wherein the Asp-Phe hybrid dipeptide synthetase comprises any Asp/Phe adenylation domain having any % sequence identity to the consensus sequences of SEQ ID NO: 1-10, any thiolation domain, any condensation domain, or thioesterase domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims. This rejection has been discussed at length in a previous Office Action mailed on 4/6/2004.

12. Applicants argue that the amended claims recite sufficient structural details of the minimal modules for recognizing Asp and Phe, so that one of skill in the art would be enabled to make and use the invention correlated to the entire scope of what is being claimed

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. For the reasons already discussed above regarding the written description rejection, one of skill in the art cannot reasonably conclude that the full scope of the claimed invention is enabled by the specification. It is reiterated herein that even if one assumes that the claims are enabled for the genus of adenylation domains required, the claims require a genus of thioesterase, thiolation and condensation domains for which no structural elements have been disclosed and the specification fails to disclose how one of skill in the art can isolate/make these domains. As such, practicing the claimed invention would require undue experimentation to determine the structures of all the thioesterase, thiolation and condensation domains which can be used in the claimed invention. In addition, the amendments made to the claims are not deemed sufficient to overcome the instant rejection in view of the fact that the term "substantial structural homology" is indefinite and the claims as written do not exclude those adenylation domains which lack structural homology to the core motifs of SEQ ID NO: 1-10. See discussion above in regard to the term "identifiable". Furthermore, even if the adenylation domains were to comprise all the core motifs of SEQ ID NO:1-10, these core motifs appear to be generic for any adenylation domain and do not present any structural features which are characteristic of adenylation domains which are specific for Asp and Phe. Therefore, in the absence of any teaching or suggestion as to which additional structural features should be present in adenylation domains specific for Asp and Phe, one of skill in the art would have to go through the burden of undue experimentation to determine which adenylation domains are suitable for the claimed invention.

Conclusion

14. No claim is in condition for allowance.

15. Applicant's amendment of claims 1-2, 4-13, 26 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

16. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
October 20, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600